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ning of each regular issue of the PCT Gazette.

(54) Title: MODIFICATION OF THE PROPERTIES OF A FIBRIN MATRIX WITH RESPECT TO GROWTH AND INGROWTH
OF CELLS

(57) Abstract: A method for modifying the properties of a fibrin matrix relative to growth and ingrowth of cells, wherein for forming the fibrin matrix a fibrinogen is used consisting of a selected fibrinogen variant or a fibrinogen enriched or depleted in a selected fibrinogen variant. In particular, the use of high-molecular weight (HMW) fibrinogen leads to a fibrin having accelerated angiogenesis properties, while the use of low-molecular weight (LMW and/or LMW') fibrinogen leads to fibrin having decelerated angiogenesis properties. The use of HMW fibrinogen when setting up angiogenesis tests results in that the tests require less time. Fibrin sealants on the basis of HMW fibrinogen can be used for burns, to promote wound healing or to inhibit scar tissue. Fibrin sealants on the basis of LMW or LMW' fibrinogen are useful to inhibit adhesions and tumor growth, for instance after surgical operations.



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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

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MEDLINE, BIOSIS, EPO-Internal, WPI Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1 142 581 A (AMERICAN NATIONAL RED CROSS) 10 October 2001 (2001-10-10) the whole document	1-24
A	WO 00 72852 A (BRISTOL MYERS SQUIBB COMPANY) 7 December 2000 (2000-12-07) the whole document	1-24
A	WO 98 55140 A (OMRIX BIOPHARMACEUTICALS) 10 December 1998 (1998-12-10) the whole document	1-24
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>HINSBERGH VAN V W M ET AL: "ROLE OF FIBRIN MATRIX IN ANGIOGENESIS". ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, NEW YORK ACADEMY OF SCIENCES, NEW YORK, NY, US, vol. 936, 2001, pages 426-437, XP008011814 ISSN: 0077-8923 the whole document</p>	1-24
A	<p>DEMPLFE C-E ET AL: "FIBRINOGEN HETEROGENEITY IN HOMOZYGOUS PLASMINOGEN DEFICIENCY TYPE I: FURTHER EVIDENCE THAT PLASMIN IS NOT INVOLVED IN FORMATION OF LMW- AND LMW'-FIBRINOGEN" THROMBOSIS AND HAEMOSTASIS, STUTTGART, DE, vol. 77, no. 5, May 1997 (1997-05), pages 879-883, XP008011824 ISSN: 0340-6245 the whole document</p>	1-24
A	<p>DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 22 March 2002 (2002-03-22) HALLEMEESCH MARCELLA M ET AL: "The turnover rate of HMW fibrinogen to LMW fibrinogen determines the plasma profile of these proteins." Database accession no. PREV200200369325 XP002226013 abstract & FASEB JOURNAL, vol. 16, no. 5, 22 March 2002 (2002-03-22), page A788 Annual Meeting of Professional Research Scientists on Experimental Biology; New Orleans, Louisiana, USA; April 20-24, 2002, March 22, 2002 ISSN: 0892-6638</p>	1-24
A	<p>COLLEN ANNEMIE ET AL: "Aberrant fibrin formation and cross-linking of fibrinogenNieuwegein, a variant with a shortened Aalpha-chain, alters endothelial capillary tube formation." BLOOD, vol. 97, no. 4, 15 February 2001 (2001-02-15), pages 973-980, XP002226021 ISSN: 0006-4971 the whole document</p>	1-24

INTERNATIONAL SEARCH REPORT

Information on patent family members

PCT/NL 03/00293

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 1142581	A	10-10-2001	EP 1142581 A2	10-10-2001
			AT 212554 T	15-02-2002
			AU 667188 B2	14-03-1996
			AU 9109391 A	25-06-1992
			CA 2097063 A1	28-05-1992
			DE 69132918 D1	14-03-2002
			DE 69132918 T2	31-10-2002
			DK 564502 T3	13-05-2002
			EP 0564502 A1	13-10-1993
			JP 6506191 T	14-07-1994
			WO 9209301 A1	11-06-1992
			US 6197325 B1	06-03-2001
			US 6117425 A	12-09-2000
			US 6054122 A	25-04-2000
			US 6559119 B1	06-05-2003
WO 0072852	A	07-12-2000	AU 5458800 A	18-12-2000
			CA 2373704 A1	07-12-2000
			EP 1187623 A1	20-03-2002
			JP 2003500170 T	07-01-2003
			NO 20015759 A	29-01-2002
			WO 0072852 A1	07-12-2000
WO 9855140	A	10-12-1998	AU 8336098 A	21-12-1998
			WO 9855140 A1	10-12-1998

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